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Section V: Multiple Myeloma

Multiple Myeloma: Future Directions in Autologous Transplantation and Novel Agents

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INTRODUCTION

Autologous hematopoietic cell transplantation (AHCT) in the 1990s and the advent of "novel" therapy, such as immune modulators and proteasome inhibitors, in the 2000s have led to impressive gains in the treatment of multiple myeloma (MM) [1,2]. In the prenovel drug era, the therapy paradigm composed of induction followed by planned AHCT in eligible patients, denoted as "upfront" or early AHCT, aimed at achieving a deeper disease response and longer survival. With modern induction therapies incorporating novel drugs, the timing and need for AHCT is increasingly debated because an additional survival benefit for early AHCT has not been established with modern induction regimens. Routine post-transplant consolidation and maintenance are new trends in AHCT-based treatment of MM. Second-generation immune modulators and proteasome inhibitors, sensitive prognostic schema, and disease-monitoring techniques are also changing the treatment landscape. This session at the tandem BMT meetings explores the relevance and future of early AHCT in MM, the role of consolidation/maintenance post-transplant, and new drug development.

EARLY AUTOLOGOUS TRANSPLANTATION FOR MYELOMA: WHAT DOES THE FUTURE HOLD?

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BENEFITS OF NEWER INDUCTION REGIMENS

Novel drug induction regimens have unseated prior conventional chemotherapy against which AHCT was proven to be superior in multiple randomized studies. Among U.S. AHCT recipients reported to the Center for International Blood and Marrow Transplant Research in 2010, 93% had received novel agent induction in the form of lenalidomide alone (16%) or bortezomib alone (31%) or both (46%). Table 1 compares the reported complete or very good partial response (CR/VGPR) rates after conventional chemotherapy versus newer induction regimens in randomized trials. Taken together, these data suggest that based on current induction practice, 35% to 60% of current AHCT recipients could be expected to be already in a VGPR or better response states before transplant. These are similar or higher than the CR/VGPR rates *after* AHCT following conventional induction.

Table 1 also suggests a response augmentation effect (of about 20% in overall CR/VGPR) after AHCT irrespective of induction regimen even in the novel era. Therefore, the most effective and rapid path to attaining maximum CR/VGPR rates for a large proportion of newly diagnosed patients is from a modern three-drug induction regimen followed by early AHCT. Similarly, the median progression-free survival (PFS) rate with the best induction regimens and AHCT (followed by maintenance) is in the >50 month range. Notably, the AHCT option was mandatory and not a randomization arm in these trials, thus preventing an analysis of its relative value in the overall scheme. These data raise more new questions (Table 2) concerning therapy in newly diagnosed MM. The best pathway for using and sequencing the three phases of modern therapy (ie, induction, intensification, and consolidation/maintenance) in newly diagnosed MM patients has not been worked out in randomized trials and is a matter of controversy. Fundamentally, the debate surrounds the value of attempting to effect deeper responses (when overall survival [OS] benefit is unproven) at the potential cost of additional therapy, toxicity, and quality of life decrement [3].

DEPTH OF RESPONSE

Given the increasing therapeutic options at relapse and a long and variable clinical course even after relapse, mortality has become (fortunately) an elusive late endpoint in modern-day induction and AHCT trials. Most trials in newly diagnosed patients use CR/VGPR rates and PFS as surrogate efficacy endpoints for OS. Notably, even in the era before novel drug induction, randomized early AHCT versus conventional therapy trials and a meta-analysis suggested a PFS benefit (in six of seven trials) or higher response rate (in all trials) for AHCT without a consistent OS benefit.

Higher CR rates are a prerequisite for eventual cure of MM, and the achievement of a deep high-quality response correlates with long-term survival [4]. A significant proportion of those in CR (35% at 11 years) may achieve a plateau in survival [5]. However, the sustainability of CR is perhaps the most important endpoint from a survival perspective. The Arkansas experience suggests that a failure to achieve a CR and especially an early loss of CR are short-term endpoints that predict inferior survival [6]. In contrast to these data, it has been demonstrated that control of MM even in the longer term is possible without achieving CR/VGPR. All MM clones are not equally aggressive, and a smoldering clinical course without ongoing therapy is possible in many who are only in a partial response.

It is reasonable to expect that the substantially higher CR rates and PFS in modern approaches may prove practically useful endpoints in conjunction with additional patient-reported QOL data. The statistical perils of a PFS as

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Table 1
Overview of Novel Agent–Based Induction with or without Early AHCT in Recent Trials

Novel Induction + AHCT Studies	Induction Regimen	Best Response Pre-AHCT (%)	Best Response Post-AHCT (%)	Survival Endpoint
HOVON-50 [24]	TAD	37 ≥ VGPR	66 ≥ VGPR	Median PFS: 34 mo*
N = 556				Median OS: 73 mo
	VAD	18 ≥ VGPR	54 ≥ VGPR	Median PFS: 25 mo
				Median OS: 60 mo
IFM 2005-01 [25]	Vel/Dex	15 CR/nCR	35 CR/nCR	Median PFS: 36 mo*
N = 482		38 ≥ VGPR	54 ≥ VGPR	3-year OS: 81 mo
	VAD	6 CR/nCR	18 CR/nCR	Median PFS: 30 mo
		15 ≥ VGPR	37 ≥ VGPR	3-year OS: 77 mo
GIMEMA MMY-3006 [15,26]	VTD	22 CR	49 CR	2-year PFS: 85%*
N = 480		62 ≥ VGPR	86 ≥ VGPR	2-year OS: 96%
	TD	5 CR	40 CR	2-year PFS: 75%
		31 ≥ VGPR	81 ≥ VGPR	2-year OS: 91%
PETHEMA/GEM05MEN0S65 [27]	TD	14 ≥ CR	37 ≥ CR	Median PFS: 28 mo
N = 386	VTD	35 ≥ CR	52 ≥ CR	Median PFS: 56 mo*
	VBMCP/ VBAD/B	21 ≥ CR	49 ≥ CR	Median PFS: 35 mo
HOVON65 GMMG HD4 [28]	PAD	42 ≥ VGPR	62 ≥ VGPR	Median PFS: 35 mo*
N = 827	VAD	14 ≥ VGPR	36 ≥ VGPR	Median PFS: 28 mo
IFM 2007-02 [29]	Vel/Dex	36 ≥ VGPR	58 ≥ VGPR	Median PFS: 30 mo
N = 199	VTD	49 ≥ VGPR	74 ≥ VGPR	Median PFS: 26 mo

Studies Not Specifying AHCT after Induction		Best Response at Four Cycles of Induction (%)	Best Response to Ongoing Non-AHCT Therapy (%)	Comment
Rajkumar et al. [12] (post hoc subgroup analysis)	Len/Dex	33% > VGPR in AHCT group	NA	3-yr OS: 92% for AHCT
		39% > VGPR in continuing therapy group	57% > VGPR in continuing therapy group	*(PFS not available)*
N = 445				3-yr OS: 79% for continuing therapy group
Richardson et al. [30]	RVD	11% > VGPR;	67% > VGPR	18-mo PFS/OS: 75% and 97%
N = 66		57% > VGPR–pre-AHCT		
Evolution [31]	CVD-mod	41% > VGPR	53% > VGPR	1-yr PFS: 100% overall
N = 140	RVD	32% > VGPR	51% > VGPR	1-yr PFS: 83%
	CVRD	33% > VGPR	58% > VGPR	1-yr PFS: 86%
Jakubowiak et al. [32]	CarfRD	44% > nCR	83% > VGPR	2-yr PFS:-92%
N = 53				

VAD indicates vincristine/adriamycin and dexamethasone; TAD, thalidomide/adriamycin and dexamethasone; T, thalidomide; VBMCP, vincristine-BCNU-melphalan-cyclophosphamide-prednisone; VBAD, vincristine-BCNU-adriamycin-dexamethasone; D or Dex, dexamethasone; Len or R, lenalidomide; Vel or V, bortezomib; C, cyclophosphamide; Carf, carfilzomib; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; HOVON, Stiching Hemato-Oncologie voor Volwassenen Nederland, Dutch-Belgian Cooperative Trial Group for Hematology Oncology; GMMG, German-Speaking Myeloma Multi-center Group; PETHEMA, Programa para el Estudio y la Terapéutica de las Hemopatías Malignas; GEM, Grupo Español de Mieloma.

* $P < .05$.

a surrogate for survival are well known. However, in diseases where long survival is expected after progression, PFS correlates very poorly with OS [7]. With the increasing availability of effective newer drugs for relapsed MM, the postprogression survival after AHCT has improved dramatically with concomitant decline in the ability of upfront treatment trials to show OS benefit.

Table 2
Important Questions in the Modern Era of Autologous Transplantation for MM

Is AHCT the best method of intensification after induction? In terms of PFS, CR rates, QOL?
How important is the goal of CR/VGPR at the individual patient level?
Is there an adequate surrogate endpoint(s) for survival benefit? CR rate? stringent CR (sCR) rate? Sustained CR rate?
Is there additional benefit to AHCT in patients who have already achieved VGPR/CR/sCR from induction?
Can similar overall outcomes be achieved with early versus delayed AHCT after modern induction?
If early AHCT is abandoned, when should hematopoietic cells be harvested?
What should the type and duration of induction therapy be in the absence of early AHCT?
Are the benefits of early AHCT similar in patients irrespective of age?
What are the pharmacoeconomic implications of the various treatment sequencing options?
What are the consequences of nonperformance of a delayed AHCT due to refractory relapse or worsening age and performance status?
Are there specific risk groups where AHCT is essential? Or avoidable?

Biologic Basis for Early Intense Therapy

MM is now recognized as a heterogeneous multiclonally evolving disease with independent clones that compete for dominance over time [8]. Clonal dynamics in MM suggest that some patients harbor stable myeloma genomes over time, whereas about one third display a pattern of linear clonal evolution. Higher risk patients have baseline clonal heterogeneity and genomic instability. Non–cross-resistant multiagent therapy aimed at inducing deep remissions and sustained over time may thus be a strategy for targeting the greater clonal heterogeneity and evolution in a significant fraction of patients. Investigators in Arkansas have pioneered this approach in their total therapy program where novel and conventional agents are used before and after AHCT. The philosophy of induction and transplant followed by consolidation/maintenance (Table 3) in most current trials are modifications of this strategy.

IS THERE A BENEFIT FOR INDIVIDUAL PATIENTS ALREADY IN CR AFTER INDUCTION?

Minimal Residual Disease after CR

Current electrophoresis-based response definitions are imperfect because MM is an incurable disease with inevitable relapse even for those in CR. Molecular and flow cytometry techniques have demonstrated the presence of significant residual MM in currently defined CR [9]. A comparison of minimal residual disease after current

Table 3
Ongoing and Planned Multicenter Randomized Trials in Newly Diagnosed MM

Study Group	Induction Choices	PBSC Collection	Intensification	Consolidation/Maintenance
BMT CTN 0702	Unspecified (any)	Postinduction	Single AHCT versus tandem AHCT vs. AHCT + RVD × 4 cycles	Lenalidomide for all patients
DFCI-IFM	RVD	After 3 cycles	AHCT vs. RVD	R
EMN02	CVD	After 3 cycles; with cyclophosphamide	AHCT single or tandem vs. VMP consolidation	RVD consolidation + lenalidomide vs. lenalidomide only
GMMG-HD5	CVD vs. PAD	After 3 cycles; with cyclophosphamide and doxorubicin	AHCT; tandem AHCT for those not in CR after AHCT1	2 cycles of lenalidomide consolidation, then lenalidomide for 2 years vs. until CR
GEM11-BENVELPRES (transplant subset)	Bendamustine + VP (BVP) × 3 cycles	AHCT followed by BVP × 2 cycles		

D or Dex indicates dexamethasone; Len or R, lenalidomide; P or V, bortezomib; C, cyclophosphamide; A, adriamycin; BMTCTN, Blood and Marrow Transplant Clinical Trials Network; GMMG, German-Speaking Myeloma Multi-center Group; EMN, European Myeloma Network; GEM, Grupo Español de Mieloma.

induction therapy and the ability of AHCT to impact such disease is lacking at this time. Because CR is such an imperfect tool in MM, one needs to consider the possibility that the consequences of CR may well vary according to myeloma genetic subtype, how the CR was defined (flow cytometry, Immune Histochemistry IHC, positron emission tomography, free light chain etc.), and how it was achieved (using novel agents only versus novel agents with high dose therapy). The Blood and Marrow Transplant Clinical Trials Network 0702 trial has a companion study that uses flow cytometric minimal residual disease assays to assess the impact of sequential multistep induction, transplant, and post-transplant therapies. In addition to quantifying the benefit of each phase of therapy, minimal residual disease data could potentially distinguish subgroups from among current responders that benefit (or not) from AHCT.

DELAYED AHCT VERSUS EARLY AHCT IN THE NOVEL AGENT ERA

All available randomized studies (from the prenovel drug era) suggest that survival is similar whether AHCT is performed early or in the delayed setting after relapse [10]. Early AHCT was associated with a longer treatment-free interval and improved QOL. In the novel drug era, randomized studies addressing this question have limited follow-up, whereas the QOL metrics as well as the "freedom from treatment" paradigm are different in the era of maintenance. In one of the few modern randomized reports available, Palumbo et al. randomized patients receiving lenalidomide-dexamethasone induction to AHCT versus melphalan-lenalidomide-prednisone combination [11]. Although CR rates and OS were similar, early AHCT reduced the risk of progression by 50% and PFS at 2 years was 73% versus 54% in favor of AHCT. A post hoc landmark analysis of the Eastern Cooperative Oncology Group E4A03 study subjects suggested that after four cycles of lenalidomide-based induction, early AHCT was associated with a higher 3-year survival (94% versus 78%) compared with continued therapy despite the excellent (57%) VGPR rates in the continuing therapy group [12].

Several ongoing studies explore the question of early versus delayed AHCT. The Intergroupe Francophone du Myélome/Dana Farber Cancer Institute (IFM/DFCI) 2009 (NCT 01208622) study randomizes subjects after three cycles of bortezomib-lenalidomide-dexamethasone (RVD) induction and stem cell collection to early AHCT with RVD consolidation (two cycles) or continued RVD (total of eight cycles). Both arms receive lenalidomide maintenance for 12 months, and subjects relapsing from the nontransplant arm are expected to receive AHCT at relapse. The European Myeloma Network 02 study (NCT 01208766) randomizes 1500 subjects after three cycles of bortezomib-cyclophosphamide-dexamethasone induction to single or tandem AHCT versus intensification with bortezomib-melphalan-prednisone followed by a second randomization to RVD consolidation

Table 4
Thalidomide Consolidation/Maintenance after AHCT

Study	Comparison	Length of Maintenance	EFS or PFS*	OS*
Attal et al. Blood 2006;108:3289-94	Thalidomide and pamidronate vs. pamidronate vs. observation†	Until progression	3-yr EFS+	4-yr OS+
Barlogie et al. Blood 2008;112: 3115-21	Thalidomide vs. no thalidomide throughout total therapy II	Until progression	5-yr EFS+	8-yr OS Trend +
Lokhorst et al. Blood 2010;115: 1113-20	Thalidomide vs. interferon	Until progression	Median EFS+	Median OS Trend −
Morgan et al. Blood 2012;119:7-15.	Thalidomide vs. observation	Until progression	Median PFS (AHCT arm)+	3-yr OS ND
Spencer et al. J Clin Oncol 2009;27: 1788-93	Thalidomide and prednisone vs. prednisone	1 yr or until progression	3-yr PFS+	3-yr OS+
Krishnan et al. Lancet Oncol 2011; 12:1195-203	Thalidomide and dexamethasone vs. dexamethasone	1 yr	3-yr PFS Trend +	3-yr OS ND
Maiolino et al. Am J Hematol 2012; 87:948-52	Thalidomide and dexamethasone vs. dexamethasone	1 yr or until progression	2-yr PFS+	3-yr OS ND
Stewart et al. Blood (abstract) 2010; 116:39a	Thalidomide and prednisone vs. observation	Until progression	4-yr PFS+	4-yr OS Trend +

EFS indicates event free survival; PFS, progression free survival; AHCT, autologous hematopietic cell Transplantation; OS, overall survival.
* + indicates favors maintenance; −, favors no maintenance; ND, no difference.
† Pamidronate and observation arms were combined for analysis.

Table 5
Lenalidomide, Bortezomib, and Zoledronate Maintenance after AHCT

Study	Comparison	Planned Length of Maintenance	TTP, EFS, or PFS*	OS*
McCarthy et al. N Engl J Med 2012;366:1770-81	Lenalidomide vs. placebo	Until progression	Median TTP, EFS, and 3-yr PFS +	Median and 3-yr OS +
Attal et al. N Engl J Med 2012; 366:1782-91	Lenalidomide vs. placebo after 2 mo lenalidomide consolidation for all	Until progression	Median PFS, EFS, and 4-yr PFS +	Median OS and 4-yr OS ND
Sonneveld et al. J Clin Oncol 2012;30:2946-55	Bortezomib-containing induction and maintenance vs. vincristine doxorubicin and dexamethasone induction and thalidomide maintenance	2 yr	Median PFS +	Median OS +
Morgan et al. Lancet 2010; 376:1989-99	Zoledronate vs. clodronate	Until progression	Median PFS (AHCT) ND	Median OS Trend + Median OS for all +

TTP indicates time to progression; EFS, event-free survival; ND, no difference.
* + indicates favors maintenance; −, favors no maintenance.

versus no consolidation. These studies incorporate risk stratification strategies that should inform us of the benefit of AHCT in specific risk subgroups.

TOXICITY, MORBIDITY, AND QOL: ARE TRANSPLANTS SAFER NOW?

The Center for International Blood and Marrow Transplant Research data suggest that day 100 mortality of upfront AHCT recipients between 2009 and 2011 is 1%. Modern better-tolerated induction regimens and advances in supportive care may have contributed to this lower incidence of serious toxicity. Many institutions routinely perform AHCT in the outpatient setting. Also in contrast to popular perception, mortality, morbidity, and societal cost from ongoing nontransplant therapy are not trivial. QOL and pharmacoeconomic considerations could become major drivers in decision making.

IS THERE AN EMERGING CONSENSUS?

In the absence of survival data and clear consensus regarding the benefits of early transplantation, the design of ongoing trials gives us an idea of what major experts in the field view as equipotent alternatives. Ongoing U.S. and European cooperative group randomized trials (Table 3) in newly diagnosed MM patients include early peripheral blood stem cell (PBSC) collection for eligible patients and the early AHCT option in at least one of the arms. After PBSC collection, for the nontransplant arm, all the trials include ongoing novel agent–based therapy (intensification and/or consolidation) followed by a lower intensity maintenance. These study designs suggest that most experts have embraced the idea of induction, PBSC harvest, intensification, and consolidation/maintenance. AHCT at this time remains the most popular and established intensification choice in the absence of evidence to the contrary. Also, it is my belief that population/registry-based studies with long-term survival outcome are needed to evaluate the overall impact of advances in each component of therapy.

CONSOLIDATION AND MAINTENANCE THERAPY AFTER UPFRONT TRANSPLANT

Philip L. McCarthy

Because most patients experience relapse and progression of MM even after AHCT, efforts have been made to consolidate and maintain response. This section focuses on the role of AHCT followed by consolidation and maintenance therapy for transplant-eligible MM patients. One of the first trials to consolidate and maintain response in MM patients was published in 1986 and used nitrosoureas, anthracyclines, alkylators, and glucocorticoids as part of induction and consolidation/maintenance therapy without improvement in OS [13]. The use of AHCT and the development of novel drugs allowed new attempts to improve, consolidate, and maintain response [1,14]. “Consolidate” is defined as therapy improving on response, and “maintenance” maintains response.

CONSOLIDATION THERAPY

Recent use of consolidation has been pioneered by the Italian Myeloma Network (Gruppo Italiano Malattie Ematologiche dell’Adulto) [15]. After tandem AHCT, the PFS for bortezomib, thalidomide, and dexamethasone (VTD) consolidation was superior to thalidomide-dexamethasone (TD) consolidation. All patients received dexamethasone maintenance therapy. The estimated 3-year OS rates were 90% and 88% for the VTD and TD arms, respectively. A recent review of the Arkansas Total Therapy (TT) approach demonstrated estimated 5-year survival rates of 57%, 65%, 68%, and 73% for TT1, TT2 without thalidomide, TT2 with thalidomide, and TT3, respectively [16]. The investigators favor the use of all effective anti-MM therapies upfront and in an intensive manner to prevent relapse/progression and improve PFS and OS.

MAINTENANCE THERAPY WITH THALIDOMIDE

Maintenance therapy should be easily delivered, convenient for the patient, result in modest or minimal toxicity, and improve PFS and ideally OS when compared with retreatment at relapse [17]. Initial maintenance trials with melphalan, interferon-α, and glucocorticoids were limited by toxicity and/or limited efficacy [18-20].

Thalidomide was considered for maintenance because it is an oral drug and was associated with induction responses. Several trials have used thalidomide as consolidation/maintenance therapy alone or with glucocorticoids until progression or for a fixed period of time after AHCT. The results of these trials with references are summarized in Table 4. All studies demonstrated that thalidomide improved

PFS and event-free survival, with mixed results with regard to OS. The lack of consistent OS benefit may be due to effective salvage therapies that can prolong OS or the inability to tolerate prolonged thalidomide therapy due to toxicity for a significant number of patients.

LENALIDOMIDE MAINTENANCE

Lenalidomide was studied in two phase III, placebo-controlled maintenance trials after AHCT: Cancer and Leukemia Group B (CALGB) 100104 and IFM 05-02. The results and references are given in Table 5. Both studies demonstrated a superior time to progression, PFS, and event-free survival. CALGB 100104 demonstrated an improved OS for the lenalidomide arm compared with the placebo arm. Most placebo arm patients crossed over to receive lenalidomide after the study was unblinded when the primary endpoint (time to progression) had been met. On an intent-to-treat analysis, the OS benefit persisted despite the cross-over. The IFM 05-02 study did not demonstrate an OS benefit, which could be due to induction treatment/consolidation differences, lenalidomide consolidation for both arms, and the use of tandem AHCT for some patients.

A two- to threefold increase was found in second primary malignancies in both studies associated with the lenalidomide arm. It is uncertain as to the exact risk factors for the development of a second primary malignancy for patients on the lenalidomide arm. The IFM investigators found a correlation with the type of consolidation pre-AHCT, age, International Scoring System stage, gender, and length of time of lenalidomide maintenance (M. Attal, unpublished observation). There were no significant pre- or post-AHCT patient characteristics for risk of second primary malignancies in the CALGB 100104 study except for lenalidomide maintenance. For the CALGB 100104 study, the cumulative incidence risk of progressive disease or death was significantly greater for the placebo arm when compared with the lenalidomide arm, and the cumulative incidence risk of second primary malignancies was significantly greater for the lenalidomide arm when compared with the placebo arm. The IFM 05-02 patients stopped lenalidomide maintenance, and CALGB 100104 patients without disease progression remain on lenalidomide.

BORTEZOMIB MAINTENANCE

Bortezomib was investigated in the Stiching Hemato-Oncologie voor Volwassenen Nederland, Dutch-Belgian Cooperative Trial Group for Hematology Oncology and German-Speaking Myeloma Multi-center Group as part of an induction regimen (bortezomib, doxorubicin, and dexamethasone) before AHCT and maintenance (every 2 weeks for 2 years) after transplant. It was compared with vincristine, doxorubicin, and dexamethasone before AHCT and maintenance with thalidomide (daily for 2 years). PFS was superior for patients receiving bortezomib as part of induction and maintenance, with an OS benefit in multivariate analysis for bortezomib induction and maintenance.

Zoledronate was compared with clodronate maintenance until progression in the MRC Myeloma IX trial. This study was composed of patients receiving and not receiving AHCT as part of treatment. PFS was not significantly different for AHCT patients receiving zoledronate when compared with those receiving clodronate. There was a trend toward an improved median OS for the zoledronate arm when compared with the clodronate arm (not reached versus 62.5 months). Data and references are summarized in Table 5.

FUTURE OF MAINTENANCE AND CONSOLIDATION

Long-term disease control remains an important goal of MM treatment. Recent clinical trials have focused on improving response as depth of response correlates with long-term outcome for patients undergoing AHCT [9,21]. MM patients who attain flow cytometric and molecular remissions have improved long-term outcomes. All ongoing trials (Table 3) that are investigating the role of early AHCT versus salvage AHCT incorporate upfront maintenance. The IFM DFCI 2009 trial has completed accrual in France and uses 1 year of lenalidomide maintenance therapy for all patients, whereas U.S. investigators will continue lenalidomide maintenance until progression/relapse. The ongoing Blood and Marrow Transplant Clinical Trials Network study incorporates 3 years of lenalidomide maintenance therapy after different intensification choices. This study will help determine the role of single versus tandem AHCT versus AHCT and consolidation therapy for newly diagnosed MM patients. The European Myeloma Network also incorporates lenalidomide maintenance therapy monthly for 3 weeks on and 1 week off until disease progression following different intensification options.

These trials will further define which MM patients will benefit from specific treatment approaches. The incorporation of new agents into induction, consolidation, and maintenance approaches should result in further improvement in PFS and OS [22]. Risk stratification will allow for patients and clinicians to determine the optimal approach for individual MM patients [23]. Prolonged treatment with induction by novel agents, consolidation before and/or after AHCT, and maintenance treatment have become the standard approach to induce an undetectable/minimal residual disease remission status that will improve long-term patient outcomes.

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